

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS,
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding Advisory Action is respectfully requested.

Attached hereto is an Appendix showing the changes made to claims 1, 138, 150, and 151, as amended.

In the Advisory Action, it is stated that the term "addressable array" in the claims has no clear support. By the above amendments to claims 1, 138, 150, and 151, the claims now indicate that the solid support and the capture oligonucleotides form an addressable array. Accordingly, any indefiniteness has been corrected.

The Advisory Action also states that there is a potential obviousness-type patenting issue relating to the claims of U.S. Patent Application Serial No. 09/440,523 and its parent U.S. Patent No. 6,027,889. Applicants respectfully disagree.

The present application was filed on February 4, 1997, and claims benefit of the February 9, 1996, filing date of U.S. Provisional Patent Application Serial No. 60/011,359. U.S. Patent Application Serial No. 09/440,523 was filed on November 15, 1999 and is a divisional of U.S. Patent Application Serial No. 08/864,473, filed May 28, 1997, which issued as U.S. Patent No. 6,027,889 on February 22, 2000. U.S. Patent Application Serial Nos. 09/440,523 and 08/864,473 both claim benefit of the May 28, 1996, filing date of U.S. Provisional Patent Application Serial No. 60/018,532. The present application has a different inventive entity from that of U.S. Patent Application Serial No. 09/440,523 and U.S. Patent No. 6,027,889.

It is well settled that an obviousness-type double patent rejection cannot be made where the claimed invention of a first patent would not have been an obvious variant of the claimed invention of a second patent application. See In re Vogel, 422 F.2d 438, 164 U.S.P.Q. 645 (CCPA 1970). To determine that the claims to a basic invention in a first filed application would have been an obvious variant of the claims directed to an improvement in an application which was filed after the first filed application but which issued first, a two-way patentability evaluation must be satisfied--i.e. it must be shown that the latter would have been obvious from the former and that the former would have been obvious from the latter. In re Braat, 937 F.2d 589, 19 U.S.P.Q. 2d 1289 (Fed. Cir. 1991). Where the application to the basic invention is filed prior to the application directed to the improvement

and the latter issues before the former, it is inappropriate to permit only a one-way patentability evaluation to be made (i.e. that either the latter would have been obvious from the former or that the former would have been obvious from the latter), because this would penalize the applicant of the case directed to the basic invention for the relatively slow progress of the earlier filed application through the U.S. Patent and Trademark Office ("PTO"). Id. See Manual of Patent Examining Procedure § 804.

The claims of the present application are directed to a basic invention for a method of detecting sequences differing by one or more single-base changes, insertions, deletions, or translocations by the use of the ligase detection reaction and the capture of the products of that reaction on a solid support with capture oligonucleotides.

By contrast, although some of the claims of U.S. Patent Application Serial No. 09/440,523 and U.S. Patent No. 6,027,889 relate to the capture of nucleic acids (derived from a ligase detection reaction) on a solid support with capture oligonucleotides, it is clear that they constitute an improvement over the basic invention and could not have been claimed in the same application without a restriction requirement being imposed. In U.S. Patent No. 6,027,889, the claims are directed to a method of detecting sequences differing by one or more single-base changes, insertions, deletions, or translocations by carrying out a ligase detection reaction followed by a polymerase chain reaction where the oligonucleotide probes for the ligase detection reaction include a 5' upstream primer-specific portion and a 3' downstream primer-specific portion to facilitate the subsequent polymerase chain reaction procedure. In U.S. Patent Application Serial No. 09/440,523, allowed claims 29-50 relate to a method of detecting sequences differing by one or more single-base changes, insertions, deletions, or translocations by carrying out a first polymerase chain reaction, a second polymerase chain reaction, and a ligase detection reaction where the polymerase chain reaction primers include a 5' upstream secondary primer-specific portion to facilitate the subsequent procedures. Claims 51-54 of U.S. Patent Application Serial No. 09/440,523 are similar, except that they do not recite a ligase detection reaction. Since the present application does not suggest the particular sequence of steps or the specific design of oligonucleotide probes or primers of U.S. Patent Application Serial No. 09/440,523 and U.S. Patent No. 6,027,889, it is clear that the claims of these cases are patentable over those of the present application. This precludes the two-way unpatentability standard from being met

and, therefore, bars any obviousness-type double patenting rejection based on U.S. Patent Application Serial No. 09/440,523 and U.S. Patent No. 6,027,889.

Applicants also wish to bring to the attention of the PTO U.S. Patent Application Serial No. 09/891,292, filed July 10, 1997, which claims benefit of U.S. Provisional Patent Application Serial No. 60/022,535, filed July 19, 1996. The claims of U.S. Patent Application Serial No. 09/891,292 have been allowed. Like U.S. Patent Application Serial No. 09/440,523 and U.S. Patent No. 6,027,889, U.S. Patent Application Serial No. 09/891,292 has an effective filing date after that of the present application with the claims of U.S. Patent Application Serial No. 09/891,292 being allowed before those of the present application. Similarly, the claimed invention of U.S. Patent Application Serial No. 09/891,292 are an improvement over that of the present invention in that the claims of the former case and could not have been pursued in one application without a restriction requirement being imposed. In particular, the claims of U.S. Patent Application Serial No. 09/891,292 are directed to detecting one or more minority target nucleotide sequences in a sample also containing one or more majority target nucleotide sequences in a ratio of less than 1:10 and more than 1:1000. Again, since these features are nowhere found in the claims of the present application, the two-way unpatentability test cannot be satisfied, precluding an obviousness-type double patenting rejection based on U.S. Patent Application Serial No. 09/891,292.

Progress of the present application through the PTO has been slow due to repeated changes in position by the prior examiner. To date, there have been 5 full office actions on the merits and one advisory action. In response, applicants have had to file 6 amendments and/or requests for reconsideration; 3 personal interviews have been held. Prosecution of U.S. Patent Application Serial No. 09/440,523 and U.S. Patent No. 6,027,889, on the other hand, was much more rapid with each case having a single office action on the merits and one amendment; the application corresponding to U.S. Patent No. 6,027,889 also had a Ex parte Quayle action and response to correct sequence informalities. U.S. Patent Application Serial No. 09/891,292 had 3 office actions, 3 responses on the merits, and 1 advisory action. It is thus apparent that, compared to the other cases noted above, prosecution of the present application has taken longer.

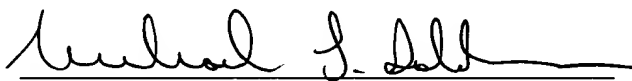
Applicants further submit that the unavailability of a double patenting rejection is entirely appropriate in this case, because, under the 20 year from filing date term

provisions of 35 U.S.C. § 154, any patent issuing from the present application will expire before any patent issuing from U.S. Patent Application Serial Nos. 09/440,523 and 09/891,292 or U.S. Patent No. 6,027,889. Accordingly, issuance of the present application would not extend the term of patent protection accorded to applicants which is the rationale for imposing a double patenting rejection. See In re Berg, 140 F.3d 1428, 46 U.S.P.Q. 2d 1226 (Fed. Cir. 1998).

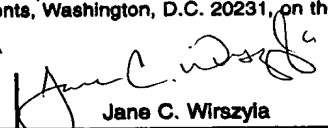
In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Dated: March 29, 2001


Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603
Telephone: (716) 263-1304
Facsimile: (716) 263-1600

Certificate of Mailing - 37 CFR 1.8(a)	
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below.	
3/29/01 Date	 Jane C. Wirszya

APPENDIX

The changes made by the amendments to claims 1, 138, 150, and 151 are shown below with insertions being underlined and deletions being bracketed.

1. (Four Times Amended) A method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising:
 - providing a sample potentially containing one or more target nucleotide sequences with a plurality of sequence differences;
 - providing a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having an oligonucleotide target-specific portion and an oligonucleotide addressable array-specific portion and (b) a second oligonucleotide probe, having an oligonucleotide target-specific portion and a detectable reporter label, wherein the oligonucleotide probes in a particular set are suitable for ligation together when hybridized adjacent to one another on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when hybridized to any other nucleotide sequence present in the sample;
 - providing a ligase[.];
 - blending the sample, the plurality of oligonucleotide probe sets, and the ligase to form a mixture;
 - subjecting the mixture to one or more ligase detection reaction cycles comprising a denaturation treatment, wherein any hybridized oligonucleotides are separated from the target nucleotide sequences, and a hybridization treatment, wherein the oligonucleotide probe sets hybridize at adjacent positions in a base-specific manner to their respective target nucleotide sequences, if present in the sample, and ligate to one another to form a ligated product sequence containing (a) the addressable array-specific portion, (b) the target-specific portions connected together, and (c) the detectable reporter label, and, wherein the oligonucleotide probe sets may hybridize to nucleotide sequences in the sample other than their respective target nucleotide sequences but do not ligate together due to a presence of one or more mismatches and individually separate during the denaturation treatment;
 - providing a solid support with different capture oligonucleotides immobilized at particular sites, wherein the capture oligonucleotides have nucleotide

sequences complementary to the addressable array-specific portions and, wherein the solid support and the capture oligonucleotides form an addressable array;

contacting the mixture, after said subjecting, with the solid support under conditions effective to hybridize the addressable array-specific portions to the capture oligonucleotides in a base-specific manner, thereby capturing the addressable array-specific portions on the solid support at the site with the complementary capture oligonucleotide; and

detecting the reporter labels of ligated product sequences captured to the solid support at particular sites, thereby indicating the presence of one or more target nucleotide sequences in the sample, wherein the oligonucleotide probe sets are configured so that the addressable array-specific portion is comprised of a nucleotide sequence which is distinct from that of the target-specific portions, in order to minimize hybridization between the target-specific portions and the capture oligonucleotides as well as between the target nucleotide sequence and the addressable array-specific portion.

138. (Thrice Amended) A kit for identifying one or more of a plurality of sequences differing by single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising:

a ligase;

a plurality oligonucleotide probe sets, each characterized by (a) a first oligonucleotide probe, having an oligonucleotide target sequence-specific portion and an oligonucleotide addressable array-specific portion and (b) a second oligonucleotide probe, having an oligonucleotide target sequence-specific portion and detectable reporter label, wherein the oligonucleotide probes in a particular set are suitable for ligation together when hybridized adjacent to one another on a respective target nucleotide sequence, but have a mismatch which interferes with such ligation when hybridized to any other nucleotide sequence, present in the sample; and

a solid support with capture oligonucleotides immobilized at particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the addressable array-specific portions, wherein the oligonucleotide probe sets are configured so that the addressable array-specific portion is comprised of a nucleotide sequence which is distinct from that of the target-specific portions, in order to minimize hybridization between the target-specific portions and the capture oligonucleotides as well as between the target

nucleotide sequences and the addressable array-specific portion and, wherein the solid support and the capture oligonucleotides form an addressable array.

150. (Amended) A method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising:

providing a sample potentially containing one or more target nucleotide sequences with a plurality of sequence differences;

providing a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having an oligonucleotide target-specific portion and an oligonucleotide addressable array-specific portion and (b) a second oligonucleotide probe, having an oligonucleotide target-specific portion and a detectable reporter label, wherein the oligonucleotide probes in a particular set are suitable for ligation together when hybridized adjacent to one another on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when hybridized to any other nucleotide sequence present in the sample;

providing a ligase[.];

blending the sample, the plurality of oligonucleotide probe sets, and the ligase to form a mixture;

subjecting the mixture to one or more ligase detection reaction cycles comprising a denaturation treatment, wherein any hybridized oligonucleotides are separated from the target nucleotide sequences, and a hybridization treatment, wherein the oligonucleotide probe sets hybridize at adjacent positions in a base-specific manner to their respective target nucleotide sequences, if present in the sample, and ligate to one another to form a ligated product sequence containing (a) the addressable array-specific portion, (b) the target-specific portions connected together, and (c) the detectable reporter label, and, wherein the oligonucleotide probe sets may hybridize to nucleotide sequences in the sample other than their respective target nucleotide sequences but do not ligate together due to a presence of one or more mismatches and individually separate during the denaturation treatment;

providing a solid support with different capture oligonucleotides immobilized at particular sites, wherein the capture oligonucleotides have nucleotide

sequences complementary to the addressable array-specific portions and, wherein the solid support and capture oligonucleotides form an addressable array;

contacting the mixture, after said subjecting, with the solid support under conditions effective to hybridize the addressable array-specific portions to the capture oligonucleotides in a base-specific manner, thereby capturing the addressable array-specific portions on the solid support at the site with the complementary capture oligonucleotide; and

detecting the reporter labels of ligated product sequences captured to the solid support at particular sites, thereby indicating the presence of one or more target nucleotide sequences in the sample, wherein sequences differing by one or more single-base changes, insertions, deletions, or translocations are discriminated from one another during the ligase detection reaction and the discriminated sequences are detected as a result of capture on the solid support.

151. (Amended) A method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising:

providing a sample potentially containing one or more target nucleotide sequences with a plurality of sequence differences;

providing a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having an oligonucleotide target-specific portion and an oligonucleotide addressable array-specific portion and (b) a second oligonucleotide probe, having an oligonucleotide target-specific portion and a detectable reporter label, wherein the oligonucleotide probes in a particular set are suitable for ligation together when hybridized adjacent to one another on a corresponding target nucleotide sequence under a single set of ligase detection reaction conditions, but have a mismatch which interferes with such ligation when hybridized to any other nucleotide sequence present in the sample;

providing a ligase[,];

blending the sample, the plurality of oligonucleotide probe sets, and the ligase to form a mixture;

subjecting the mixture to one or more ligase detection reaction cycles comprising a denaturation treatment, wherein any hybridized oligonucleotides are separated

from the target nucleotide sequences, and a hybridization treatment, wherein the oligonucleotide probe sets hybridize at adjacent positions in a base-specific manner to their respective target nucleotide sequences, if present in the sample, and ligate to one another to form a ligated product sequence containing (a) the addressable array-specific portion, (b) the target-specific portions connected together, and (c) the detectable reporter label, and, wherein the oligonucleotide probe sets may hybridize to nucleotide sequences in the sample other than their respective target nucleotide sequences but do not ligate together due to a presence of one or more mismatches and individually separate during the denaturation treatment;

providing a solid support with different capture oligonucleotides immobilized at particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the addressable array-specific portions and, wherein the solid support and capture oligonucleotides form an addressable array;

contacting the mixture, after said subjecting, with the solid support under conditions effective to hybridize the addressable array-specific portions to the capture oligonucleotides in a base-specific manner, thereby capturing the addressable array-specific portions on the solid support at the site with the complementary capture oligonucleotide; and

detecting the reporter labels of ligated product sequences captured to the solid support at particular sites, thereby indicating the presence of one or more target nucleotide sequences in the sample.